005699-022

PATENT SPECIFICATION (11) 1 505 633

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(21) Application No. 52802/76 (22) Filed 17 Dec. 1976
(31) Convention Application No. 643211
(32) Filed 22 Dec. 1975
(31) Convention Application No. 734160
(32) Filed 20 Oct. 1976 in
(33) United States of America (US)
(44) Complete Specification published 30 March 1978
(51) INT CL² C07C 103/76
(52) Index at acceptance
C2C 220 227 22Y 280 281 29X 29Y 30Y 315 31Y 321 32Y 342 34Y 364 36Y 449 579 57X 57Y 583 620 62X 630 63X 64X 660 669 KJ KZ

(19)

(54) 3,5-BIS(ACYLAMINO)BENZAMIDES

(71) We, MALLINCKRODT, INC., a Corporation organised and existing under the laws of the State of Missouri, United States of America, 675 Brown Road, St Louis, State of Missouri 63134, United States of America, (formerly of P.O. Box 5439, St. Louis, State of Missouri 63147, United States of America), do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to 3,4 - bis(lower acylamino) - benzamides which are useful as intermediates in the preparation of 3 - (lower acylamino) - 5 - amino - 2,4,6 - triiodobenzamides, and to methods for making and using such compounds.

Certain 3,5 - disubstituted, 2,4,6 - triiodoanilides of polyhydroxymonobasic acids have recently been found useful as non-ionic X-ray contrast agents. Among such compounds, for example, are 3 - gluconamido - 5 - [N - (2 - hydroxyethyl) acetamido] - 2,4,6 - triiodo - N - methylbenzamide and 3 - gluconamido - N - (2 - hydroxyethyl) - 2,4,6 - triiodo - 5 - (N - methylacetamido)benzamide (W. German Offenlegungsschrift 2,456,685).

In the preparation of such iodinated nonionic X-ray contrast agents a 3 - (lower acylamino) - 5 - amino - 2,4,6 - triiodobenzamide is a key intermediate. Such intermediates have been prepared from commercially available 3,5 - dinitrobenzoic acid by a series of reactions of which the following six step sequence is illustrative:

3,5 - dinitrobenzoic acid (I)→3 - amino - 5 - nitrobenzoic acid (II)→3 - acetamido - 5 - nitrobenzoic acid (III)→3 - acetamido - 5 - aminobenzoic acid (IV)→3 - acetamido - 5 - amino - 2,4,6 - triiodobenzoic acid (V) →3 - acetamido - 5 - thionoylamino - 2,4,6 - triiodobenzoylchloride (VI)→3 - acetamido - 5 - amino - 2,4,6 - triiodo - N - methylbenzamide (VII).

It will be appreciated that this reaction is quite complex. The yields are poor and substantial purification procedures are required. The cost to operate this reaction commercially would be quite high.

A two step method for preparing compound IV from compound I is disclosed in British Patent Specification No. 1,374,338. This involves the sequence:

I→3,5 - diaminobenzoic acid (VIII)→IV.

Compound VIII is dissolved in an aqueous mineral acid solution and acetic anhydride, (molar ratio 1—1.7 with respect to VIII) added in the cold, whereby compound IV precipitates in the form of its mineral acid salt, from which the free acid is liberated by treating the salt was a base.

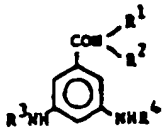
W. German Offenlegungsschrift 2,424,197 discloses a two step method for preparing compound V from compound VIII. This involves the sequence:

VIII→3,5 - bis - acetamidobenzoic acid (IX)→V.

A hot aqueous suspension of compound VIII is treated with acetic anhydride (molar ratio 2.5 with respect to VIII) to form compound IX, which precipitates when the solution cools. The reaction mixture is then acidified, treated with $NaIO_2$ solution, and heated. Upon cooling, compound V precipitates.

Although this is an improved method for obtaining compound V, the steps still required to go from V to VII are complex and result in poor yields and low quality product.

The present invention provides a benzamide having the general formula:—



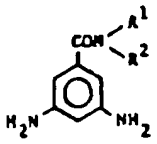
wherein R^1 and R^2 are each independently a hydrogen atom or a lower alkyl group: and R^3 and R^4 are each independently a lower alkanoyl or lower alkoxy - (lower alkanoyl) group.

By using the procedure of the present invention yields are substantially increased, the number of reaction steps reduced and purification procedures greatly simplified. Thus, the overall cost of the reaction is such that it would be attractive on a commercial basis. Furthermore, it was unexpected that a 3,5 - bis - acylamino - benzoic acid amide could be iodinated. It was thought that a free amino group was needed on the benzoic acid amide to bring about iodination.

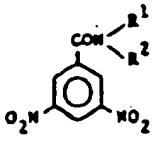
By the term "lower" (e.g. lower alkyl, lower acyl) is meant that the group referred to contains between one and six carbon atoms. Furthermore, the term "lower acyl" is intended to cover lower alkanoyl, i.e. acetyl, propionyl, etc., and lower alkoxy - (lower alkanoyl), i.e. methoxyacetyl, ethoxyacetyl, methoxypropionyl, etc.

The 3,5 - bis - (lower acylamino)benzamides of the present invention are prepared by first hydrogenating a 3,5 - dinitrobenzamide to form the 3,5 - diaminobenzamide which is then acylated to form the 3,5 - bis - (acylamino)benzamide.

More particularly, a 3,5 - diaminobenzamide having the general formula:

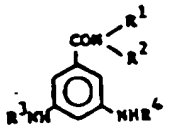


wherein R^1 and R^2 are each independently a hydrogen atom or a lower alkyl group, is prepared by hydrogenating a compound having the general formula:

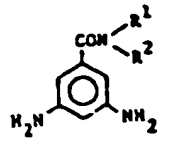


wherein R^1 and R^2 are as defined above, to form the corresponding 3,5 - diaminobenzamide.

An acylated 3,5 - diaminobenzamide represented by the formula



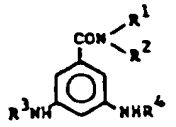
wherein R^1 and R^2 are each independently a hydrogen atom or a lower alkyl group, and R^3 and R^4 are lower acyl groups, is prepared by reacting a 3,5 - diaminobenzamide of the formula:



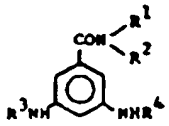
wherein R^1 and R^2 are as above defined with an acylating agent to form the acylated 3,5 - diaminobenzamide.

By the term "acylating agent" as used herein is meant a substance capable of reacting with an aromatic amino group to form an alkanoylamino group (e.g., acetamido, propionamido, etc.) or an alkoxy - alkanylamino group (e.g., methoxylacetamido, ethoxyacetamido, 3 - methoxypropionamido, etc.). Such agents include, for example, acid anhydrides (e.g., acetic anhydride, propionic anhydride, etc.) and acyl halides (e.g., acetyl chloride, propionyl bromide, methoxyacetyl chloride, etc.).

In accordance with a further aspect of the present invention the 3 - (lower acylamino) - 5 - amino - 2,4,6 - triiodomenzamide having the general formula:



wherein R^1 and R^2 are each independently a hydrogen atom or a lower alkyl group and R^4 is a lower acyl group, are prepared by treating a lower acylamino - benzamide having the general formula:



wherein R^1, R^2 and R^4 are as defined above, and R^3 is a lower acyl group, with an iodinating agent in an aqueous medium, advantageously under acid conditions to form the 3 - (lower acylamino) - 5 - amino - 2,4,6 - triiodobenzamide.

Illustrative of iodinating agents which may be used are solutions of iodine, iodine monocholride, $HICl_2$, sodium iodochloride and potassium iodochloride.

Another embodiment of this invention, is directed to a method for preparing a 3 - (lower acylamino) - 5 - amino - 2,4,6 - triiodobenzamide which comprises hydrogenating a 3,5 - dinitrobenzamide to form a 3,5 - diaminobenzamide, reacting the 3,5 - di-

aminobenzamide with an acylating agent to form an acylated 3,5 - diaminobenzamide, and reacting the acylated 3,5 - diaminobenzamide with an iodinating agent in an aqueous medium, advantageously under acid conditions to form the 3 - lower acylamino) - 5 - amino - 2,4,6 - triiodobenzamide.

Among the compounds within the scope of the invention, the following may be mentioned by way of example:

3,5 - bis - acetabido - N,N - dimethylbenzamide
3,5 - bis(methoxyacetamido) - N - methylbenzamide
3,5 - bis - acetamido - N - (propyl)-benzamide
3,5 - bis - acetamido - N,N - diethylbenzamide

The hydrogenation of the 3,5 - dinitrobenzamide is preferably carried out in a solution of the dinitrobenzamide in a solvent therefore fhich is not readily reduced by hydrogen, such as a lower alkanol (e.g., methanol, ethanol, etc.), a lower aliphatic ester (e.g. ethyl acetate), or a lower aromatic hydrocarbon (e.g. toluene). It may also be effected in slurries of the dinitrobenzamide in water and hydrochloric acid whereby as reduction progresses it forms an amine hydrochloride and solution is effected. The hydrogenation of the dinitrobenzamide is preferably accomplished with hydrogen at an elevated pressure in the presence of a hydrogenation catalyst such as Raney nickel, or preferably, a supported noble metal catalyst, such as 5% platinum or palladium on carbon. The actual pressure is not critical but hydrogen pressures in the range of about 10 to about 50 psig are suitable.

After the theoretical amount of hydrogen has been taken up, the catalyst is filtered off, and the 3,5 - diaminobenzamide may be isolated, as such, by evaporating the solvent.

Alternatively, the nitro functions may be reduced to amino functions by means of a reducing/hydrogenating agent such as iron and hydrochloric acid or tin and hydrochloric acid.

Preferably, the diamine is converted to the dihydrochloride or other acid addition salt. This may be accomplished, for example, by passing dry hydrogen chloride into the solution of the diamine, to precipitate the dihydrochloride, or by mixing the solution of the diamine with an excess of aqueous hydrochloric acid solution and evaporating the resulting solution to dryness.

The acylation of the 3,5 - diaminobenzamide is most conveniently carried out by first preparing an aqueous solution of the diamino compound, in the form of a salt. If the diamino compound is isolated as a salt (such as the dihydrochloride) following the hydrogenation reaction, this salt may simply be dissolved in water. On the other hand, if the diamino compound is isolated as the free amine it may be dissolved in water containing sufficient acid, suitably hydrochloric or other common mineral acid, to accomplish solution of the amine. The acylation is preferably carried out at a reduced temperature to minimize hydrolysis of the acylating agent by water. Preferably the temperature should be below approximately 30°C. The acylating agent is preferably added in small portions to the cooled solution of the diamine. Alternatively, the diamine may be dissolved in a suitable organic solvent, such as ethyl acetate, toluene, etc., and the acylating agent added to this solution. In certain instances, the acylating agent itself (e.g. acetic anhydride) may serve as a solvent/reaction medium for the diamine.

The degree of acylation of the diamine is dependent upon the relative amount of acylating agent added. Ordinarily, if the molar ratio of acylating agent to diaminobenzamide is in the range of about 1 to about 1.5, the product consists primarily of the monoacylamino derivative. As the proportion of acylating agent increases, the proportion of bis - acylamino derivative in the product increases. Use of about 2 to about 4 mols. of acylating agent per mol. of diaminobenzamide yields a product which is primarily the bis-acylamino derivative, with varying lesser amounts of the monoacylamino derivative.

As noted previously, the invention, in its method aspect, relates to the iodination of an acylated 3,5 - bis - (lower acylamino)benzamide to yield a 3 - (lower acylamino) - 5 - amino - 2,4,6 - triiodobenzamide. The iodination is accompanied by the deacylation of one acylamino group to form the desired 3 - (lower acylamino) - 5 - amino - 2,4,6 - triiodobenzamide. It is carried out in the usual manner employing a sufficient amount of the iodinating agent to bring about triiodination. Preferably, it is carried out in an aqueous medium under acid conditions, i.e. at an acid pH from below 1 to about 6 at the iodinating temperature, i.e. 20 to 85°C. For example when utilizing sodium iododichloride ($NaICl_2$) about 3 equivalents is used per equivalent of the 3,5 bis(lower acylamino) benzamide. It is generally added as a 2.4N solution over a period of 1 to 30 minutes to the acylamino benzamide in an aqueous medium. The mixture is agitated for 2 to 15 hours and the iodination is completed by warming at 65 to 85°C. for 4 to 10 hours.

It is noted that, in accordance with nomenclatural convention, in a benzamide either position on the ring that is *meta* to the carboxamide function may be assigned to the number "3", in which cse the other *meta*

position is assigned to the number "5". It is further noted these number assignments are sometimes reversed more or less arbitrarily to accomplish a particular nomenclatural purpose.

The invention is further illustrated by the following examples. Example 1 illustrates the preparation of an intermediate derivative.

Example 1

3,5 - Diamino - N - methylbenzamide Dihydrochloride

3,5 - Dinitro - N - methylbenzamide (0.1 mol: 22.5g.) was slurried in methanol, and the slurry and reaction vessel was purged with nitrogen. Catalyst (5% Pd/C; 3.0 g.) was added, and reduction of the nitro groups was carried out with hydrogen at elevated pressures (10—50 psig). The theoretical amount of hydrogen (0.6 mol) to form 3,5 - diamino - N - methyl - benzamide was taken up in the reaction. The catalyst was filtered off, and the filtrate was run into a solution of hydrochloric acid (20 ml water+20 ml conc. acid; 0.2 mol HCl). The resulting solution was evaporated to dryness under reduced pressure, leaving a residue of 3,5 - diamino - N - methylbenzamide dihydrochloride.

Example 2

3,5 - Bis - acetamido - N - methylbenzamide

3,5 - Diamino - N - methylbenzamide dihydrochloride (0.1 mol), prepared as described in Example 1, was dissolved in water (750 ml) at 25°C. Acetic anhydride (0.25 mole; 25 g) was added during a 20 minute period. The solution was stirred for 45 minutes, and additional acetic anhydride (0.05 mol; 5 g) was added. Stirring was continued for an additional 45 minutes, after which another aliquot of acetic anhydride (0.05 mol; 5 g) was added, and stirring was continued for an additional 40 minutes. TLC (25:5:1, Chloroform:Methanol:Ammonia) examination of the reaction mixture indicated that the crude product was predominantly 3,5 - bis - acetamido - N - methylbenzamide, with about 5—10% 3 - acetamido - 5 - amino - N - methylamide.

Example 3

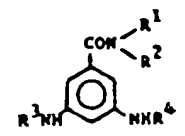
Preparation of 3 - Acetamido - 5 - amino - 2,4,6 - triodo - N - methylbenzamide from 3,5 - bis - acetamido- N - methyl - benzamide

The reaction mixture from Example 2 was diluted with water (250 ml.) and heated to 45—50°C. A solution of 2.4 *N* NaICl (0.33 mol; 138 ml) was added during a 30 minute period. The reaction mixture was cooled to 25°C. and stirred overnight. The slurry was heated to 70—72°C. and stirred for 6.5 hours and then was cooled to 30°C. and filtered. The solids were first re-slurried in water (200 ml) for four hours, then twice under reflux in methanol (150 ml) for four hours. The light tan solid was air dried overnight to yield 41.0 g. (70.1% of product. NMR and IR spectra and TCL analysis (25:5:1, Chloroform:Methanol:Ammonia) indicated that the product was predominantly 3 - acetamido - 5 - amino - 2,4,6 - triiodo - N - methylbenzamide. The TLC results indicated the presence of a small proportion (estimated to be <2%) of material of lower R_f, speculated to be a diiodo compound, as well as a small proportion (estimated to be <2%) of material of higher R_f, speculated to be 3,5 - diamino - 2,4,6 - triiodo - N - methylbenzamide.

Compounds within the scope of the invention other than those specifically disclosed in the preceding examples may be prepared by similar methods. For example, the treatment of a solution of a 3,5 - diaminobenzamide, such as 3,5 - diamino - N - methylbenzamide, with a lower alkoxy - (lower acyl) halide, such as methoxyacetyl chloride, under conditions generally similar to those described above, results in the formation of a mixture of acylated products containing varying proportions of the 3 - amino - 5 - (lower alkoxy - lower acylamino) - benzamide (e.g., 3 - amino - 5 - methoxyacetamido - N - methylbenzamide) and of the 3,5 - bis - (lower alkoxy - lower acylamino) benzamide (e.g., 3,5 - bis(methoxyacetamido) - N - methylbenzamide, depending on the proportions of the 3,5 - diaminobenzamide and the acylating agent employed. The diacylated product may then be iodinated under the conditions generally described above with the resultant formation of the corresponding 3 - amino - 5 - (lower alkoxy - lower acylamino) - 2,4,6 - triiodobenzamide (e.g., 3 - amino - 5 - methoxyacetamido - 2,4,6 - triiodo - N - methylbenzamide).

WHAT WE CLAIM IS:—

1. A benzamide having the general formula:



wherein R^1 and R^2 are each independently a hydrogen atom or a lower alkyl group; and R^3 and R^4 are each independently a lower alkanoyl or lower alkoxy - (lower alkanoyl) group.

2. A compound as claimed in claim 1 wherein R^3 and R^4 are each independently an acetyl, propionyl, methoxyacetyl, ethoxyacetyl or methoxypropionyl group.

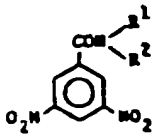
3. A compound as claimed in claim 2

wherein R^1 is a hydrogen atom and R^2 is a lower alkyl group.

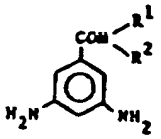
4. A compound as claimed in claim 3 wherein R^2 is a methyl group.

5. A compound as claimed in claim 3 or claim 4 wherein R^3 and R^4 are acetyl groups.

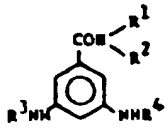
6. A process for preparing a compound as claimed in claim 1 which comprises hydrogenating a 3,5 - dinitrobenzamide having the general formula:



wherein R^1 and R^2 are as defined in claim 1 to form a 3,5 - diaminobenzamide having the general formula:



wherein R^1 and R^2 are as defined in claim 1 and acylating said compound to form an acylated 3,5 - diaminobenzamide having the general formula:

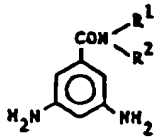


wherein R^1, R^2, R^3 and R^4 are as defined in claim 1.

7. A process as claimed in claim 6 substantially as hereinbefore described.

8. A compound as claimed in claim 1 whenever prepared by a process as claimed in claim 6 or claim 7.

9. A process for the preparation of a 3 - (lower acylamino) - 5 - amino - 2,4,6 - triiodobenzamide having the general formula:



wherein R^1, R^2 and R^4 are as defined in claim 1, which process comprises reacting an acylated 3,5 - diaminobenzamide as claimed in any one of claims 1 to 5 in an aqueous medium with an iodinating agent under acid conditions.

10. A process as claimed in claim 9 wherein the iodinating agent is iodine, iodine monochloride, $HICl_2$, sodium icododichloride or potassium icododichloride.

11. A process as claimed in claim 10 wherein the iodinating agent is sodium iodochloride.

12. A process as claimed in claim 9 substantially as hereinbefore described.

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Chartered Patent Agents,

Printed for Her Majesty's Stationery Office, by the Courier Press, Leamington Spa, 1978
Published by The Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.